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Concerns about efficacy of deep brain stimulation (DBS) in centromedian-parafascicular thalamic complex for rapid onset dystonia-parkinsonism (DYT12-ATP1A3)

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Dear Editor,

We read with significant interest Wang et al.'s paper titled "Centromedian-Parafascicular Complex Deep Brain Stimulation Improves Motor Symptoms in Rapid Onset Dystonia-Parkinsonism (DYT12-ATP1A3)," recently published in *Brain Stimulation* [1]. This article caught our attention given the lack of proven efficacy of both pharmacological and neurosurgical treatments for alleviating rapid-onset dystonia-parkinsonism phenotype related to ATP1A3 gene pathogenic variants [2], currently referred to as DYT/PARK-ATP1A3 [3]. Although pallidal DBS is efficient in both dystonia and parkinsonism due to other genetic conditions [4], the overall evidence supports a less beneficial effect [5] or a failure of DBS targeting various anatomical structures in DYT/PARK-ATP1A3, usually leading to the decision to abstain from using DBS in patients with severe DYT/PARK-ATP1A3 (personal notes and correspondences with expert centers in the field of movement disorders and DBS). Thus, we are motivated to discuss this first case further, reporting a positive outcome following DBS to the Centre Median-Parafascicularis complex (CM-Pf) of the thalamus. We comment on three key aspects of this report: i) the history and phenomenology of the movement disorder and clinical presentation, ii) the choice of the DBS target, and iii) DBS settings programming.

The authors describe a 14-year-old male presenting with a gradually worsening complex movement disorder instead of the classic abrupt onset commonly seen in DYT/PARK- ATP1A3. The onset symptom was bilateral lower limb weakness preventing gait three months before the occurrence of cranial involvement altering speech and swallowing and subsequent rostro-caudal development. Left hemibody prominent daily multiple paroxysmal dystonia episodes lasting for minutes were associated with persistent phenomenology. However, the baseline video sequence did not capture them. Generalized dystonia associated with severe global bradykinesia without obvious decrement (the short duration of the maneuvers limited the assessment) and right arm dystonic tremor are illustrated. The case description addressed neither developmental milestones in infancy and childhood nor the patient's medical history before the occurrence of weakness, information that could have added significant value to phenotype characterization. An illustration of the motor skills achieved, including speech before the movement disorder onset and paroxysmal dystonia episodes, would have supported and completed the depiction of motor phenomenology. Intellectual disability and deterioration were noted. Reporting assessment time points and the deficits in different cognitive domains and measurements supporting them, along with eventual psychiatric comorbidity, would have permitted the completion of the syndromic description. Family history and molecular analysis further to the index case are lacking. Based on the case description, an intermediate phenotype with features overlapping the two major phenotypes related to ATP1A3 gene pathogenic variants, rapid-onset dystonia-parkinsonism (RDP), and alternating hemiplegia of childhood (AHC), may be considered [6,7]. Completing the phenotype description would further the discussion of whether a phenotype with overlapping phenomenology, including paroxysmal dystonia, is preferable for explaining DBS efficacy. The presented case possibly underwent DBS early—three months after the movement disorder onset. Another important question this case raises is whether the time from symptom onset to DBS surgery is critical for DBS responsiveness in ATP1A3-related movement disorders.

The second key aspect of the article concerns the surgical procedure and the choice of DBS targets. The initial choice of the subthalamic nucleus (STN) deserves argumentation and should be questioned as paroxysmal dystonia is the most commonly reported phenomenology. As early as after the one-week STN DBS trial, which was assessed as ineffective, the authors considered the Centre Median-Parafascicularis (CM-Pf) complex of the thalamus a promising target, based on their experience, experience which unfortunately was not disclosed in the manuscript. Whether the two STN leads remained active or were replaced by the leads in the CM-Pf is unclear. The caudal aspect of the thalamic intralaminar nuclei has strong projections to the basal ganglia nuclei and reciprocal connections with the cerebral cortex. Therefore, the CM-Pf complex occupies a crucial position in modulating the functioning of various cortical–subcortical circuits in many domains, including the sensorimotor domain [8]. Receiving strong input from the globus pallidus pars interna (GPi) and sending glutamatergic output to the STN, the CM-Pf complex has been recommended as an alternative target for rest tremors or dopa-induced dyskinesia in Parkinson's disease (PD) [9]. Although DBS of the CM-Pf may benefit treatment-refractory pain, epilepsy, and Gilles de la Tourette syndrome, it may have a limited demonstrated role in the treatment of movement disorders,

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including PD [8]. A rationale for this indication, including experience of the authors implanting this target together with the stereotactic coordinates of the selected target, and an illustration showing the lead artifacts on a postoperative CT or MRI (instead of the provided illustration), would have provided the reader with sufficient support, given the variability of stereotactic coordinates between studies and the anatomical differences of these nuclei.

The third key aspect of the article relates to DBS programming. Following an ineffective STN DBS trial with high-frequency bipolar stimulation (contact E0-and E3 +), a one-week CM-Pf stimulation testing period was programmed with bilateral stimulation, 130 Hz frequency, 90 microseconds pulse width, and 3 V and 3.5 V, respectively, leading to a significant improvement in motor symptoms, especially in the left limbs. DBS settings were altered with bilateral cathodal double-monopolar stimulation at the last reported follow-up. The choice of bipolar stimulation in acute settings for concluding ineffective STN DBS and an effective CM-Pf DBS deserves further discussion, as does the argument for cathodal DBS at the last reported follow-up.

The positive results following CM-Pf DBS in a patient with DYT/PARK-ATP1A3 that the authors presented [1] are even more relevant given that only negative outcomes were reported following DBS targeting the major structures used in movement disorders.

The respective roles of the clinical presentation with an intermediate phenotype and the paroxysmal dystonic component, and the choice of the CM-Pf complex as a target in early surgery following disease onset [10] (three months compared to several years), leading to a positive outcome, unlike the previously reported negative outcomes of DBS in DYT/PARK- ATP1A3, have yet to be clarified and supported by further observations. Hopefully, future research will indicate if CM-Pf can be an alternative DBS target for patients with DYT/PARK- ATP1A3.

CRediT authorship contribution statement

Laura Cif: Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Mayté Castro Jimenez:** Writing – review & editing, Validation, Methodology, Conceptualization. **Julien F. Bally:** Writing – review & editing, Validation, Methodology, Conceptualization.

Declaration of competing interest

Dr. Cif received consulting honoraria for educational activities from Boston Scientific and support from Canadian Dystonia Research Foundation outside the submitted work.

Dr. Castro Jimenez has no competing interests to declare.

Dr. Bally participated to advisory boards and/or received honoraria for educational activities and speaker fees from Spirig, Bial Switzerland, AbbVie, Merz and Zambon.

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